



Europäisches Patentamt

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⑪ Publication number:

0 264 231

A1

⑫

EUROPEAN PATENT APPLICATION

⑬ Application number: 87308942.9

⑮ Int. Cl. 1: C07D 205/08, A61K 31/395

⑭ Date of filing: 09.10.87

⑯ Priority: 17.10.86 JP 246638/86

⑰ Applicant: TAISHO PHARMACEUTICAL CO. LTD

⑰ Date of publication of application:
20.04.88 Bulletin 88/16

24-1 Takata 3-chome Toshima-ku
Tokyo 171(JP)

⑯ Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

⑰ Inventor: Kawashima, Yutaka
1731-1, Akoda
Tatebayashi-shi(JP)

Inventor: Satoh, Masakazu

Ekimae Puraza 6-205 15-1, Akamidai-2-chome
Konosu-shi(JP)

Inventor: Hatada, Yulchi
8-17, Minamimagome-4-chome Ota-ku
Tokyo(JP)

Inventor: Hazato, Fumiko
Kopo Sanraiizu 203 41-7, Haraichi
Ageo-Shi(JP)

Inventor: Nakashima, Yoshimoto
18-16, Gobancho
Ageo-shi(JP)

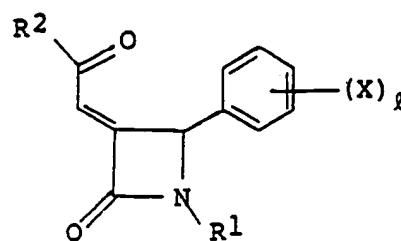
Inventor: Sota, Kaoru
1158-11, Shimotomi
Tokorozawa-shi(JP)

⑰ Representative: Ellis, Edward Lovell et al
MEWBURN ELLIS & CO. 2/3 Cursitor Street
London EC4A 1BQ(GB)

⑯ Azetidinone derivatives.

⑯ 2-Azetidinone derivatives represented by the following formula

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wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, l is 1 or 2, R1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, an

optionally substituted phenethyl group, an optionally substituted phenyl group, an optionally substituted benzyl group or a bis(alkoxycarbonyl)ethyl group, and R² is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxy carbonylmethyl group or an optionally substituted phenyl group, are useful as blood platelet aggregation inhibiting agents.

AZETIDINONE DERIVATIVES

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

5 The present invention relates to 2-azetidinone derivatives having blood platelet aggregation inhibiting activity.

10 2. DESCRIPTION OF THE PRIOR ART

Although some compounds having azetidinone skeleton which show antibacterial activity have been known in the past, any azetidinone derivative showing blood platelet aggregation inhibiting activity has not been yet reported.

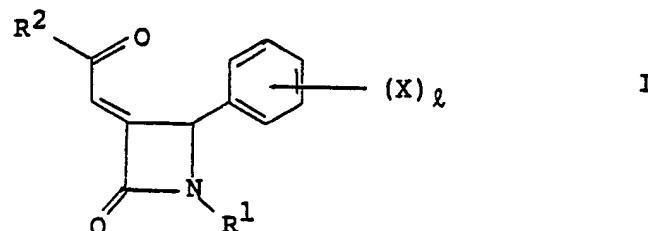
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SUMMARY OF THE INVENTION

20 As a result of earnest researches to blood platelet aggregation inhibiting activity of the compounds having an azetidinone skeleton, the present inventors have found novel 2-azetidinone derivatives having blood platelet aggregation inhibiting activity, and the present invention has been completed.

An object of the present invention is to provide 2-azetidinone derivatives represented by the general formula

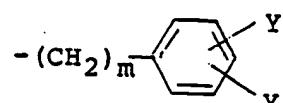
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35 wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, l is 1 or 2, R1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula

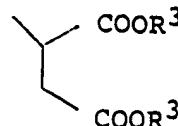
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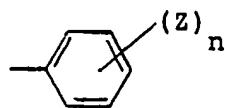
(wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula

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(wherein R^3 is a lower alkyl group), and R^2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxy carbonylmethyl group, a group of the formula

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10 (wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

Other object of the present invention is to provide blood platelet aggregation inhibiting agents containing the compound of formula I.

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DETAILED DESCRIPTION OF THE INVENTION

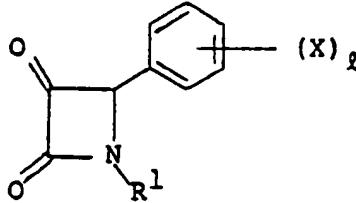
In the present invention, the term "lower alkyl group" refers to straight or branched chain alkyl group having 1 to 4 carbon atoms such as, for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a tert-butyl group and the like. The term "cycloalkyl group" refers to a cyclopentyl group and a cyclohexyl group. The term "lower alkoxy group" refers to those having 1 to 3 carbon atoms such as, for example, a methoxy group, an ethoxy group, a propoxy group and the like. The term "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. The term "lower alkoxy carbonylmethyl group" refers to those such as, for example, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group and the like.

20 Preferred compounds of formula I are those wherein X is a hydrogen atom, R^1 is a benzyl group or a chlorobenzyl group, and R^2 is a nitrophenyl group.

The compounds of the present invention can be easily prepared, for example, by a reaction (i.e., Wittig Reaction) of a compound represented by the general formula

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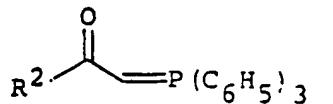


II

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wherein R^1 , X and t are as defined above, with a Wittig reagent represented by the general formula

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III

wherein R^2 is as defined above.

Reaction solvents used in this reaction are those used in the ordinary Wittig Reaction such as, for example, benzene, ethyl ether, tetrahydrofuran, toluene, chloroform, methylene chloride, dimethoxyethane and the like. The reaction temperature is from -30°C to the temperature of the boiling point of the solvent used, preferably from 0°C to 30°C. The reaction time depends on the starting material, the Wittig reagent or the reaction temperature, but usually it is from 2 to 48 hours, and the reaction may be stopped after the disappearance of the starting material observed by using thin layer silica gel column chromatography.

50 Configuration of the oxyalkylidene substituent of especially useful compounds of the present invention is E-form, and the configuration due to the asymmetric carbon atom at the 4-configuration is di-form.

Some of the compounds of formula II are known, and some are new and can be prepared by the methods described in the literature [e.g., Tetrahedron Letters, Vol. 25 (No. 42), page 4733 (1984)].

It is recognized that the compounds of the present invention have excellent blood platelet aggregation inhibiting activity and very poor bleeding tendency as side-effect, and therefore, they are useful as blood platelet aggregation inhibiting agents. For the purpose, these compounds can be administered orally or parenterally in a conventional dosage form such as tablets, powders, granules, capsules, solutions, emulsions, suspensions, injectional solutions and the like, each of which can be prepared by conventional pharmaceutical practices.

5 The dosage used as blood platelet aggregation inhibiting agents to human depends on the age, weight or response of patient, administration route or time of administration, but usually it may be from 10 to 3000 mg per day.

10 The LD₅₀ of the compound of formula I in mouse is more than 5000 mg/kg.

Next, the following experiments illustrate concretely excellent blood platelet aggregation inhibiting activity and prolongation effect of bleeding time of the compound of the present invention.

15 Experiment 1 [invitro test in rabbit]

Citrated blood (one volume of 3.2% sodium citrate; 9 volumes of blood) was collected from carotid artery of male, New Zealand strain house rabbit, centrifuged at 150 g for 15 minutes to give platelet rich plasma (PRP) as a supernatant, and the remaining blood was centrifuged at 1500 g for 10 minutes to give 20 platelet poor plasma (PPP) as a supernatant. The platelet count of PRP was adjusted to $50 - 60 \times 10^6/\mu\text{l}$ by dilution of PPP. Blood platelet aggregation was carried out according to the method of Born [Born, G.V.R., Nature, 194, 927 (1962)]. Namely, 25 μl of the test drug, (all the test drugs were dissolved in dimethyl sulfoxide and adjusted to the desired concentration with physiological saline solution), was added to 250 μl of PRP, and the mixture was incubated at 37°C for 3 minutes. 25 μl of the aggregation inducing substance 30 [adenosine diphosphate (ADP); final concentration 5 μM or collagen; final concentration 5 $\mu\text{g/ml}$] was added, the mixture was measured for 5 minutes by blood platelet aggregation ability measurement apparatus (Aggricoda TM-PA-3210, Kyoto Dai-ichi Kagaku) to obtain the maximum aggregation rate, and there was calculated the concentration of the test drug (IC_{50}) which brings about 50% inhibition to the maximum aggregation rate obtained by adding the aggregation inducing substance to PRP containing the solvent only.

The compound numbers in Table 1 correspond to those in the Examples described below.

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Table 1

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Compound No.	IC ₅₀ (x μM)		Compound No.	IC ₅₀ (x μM)	
	ADP	Collagen		ADP	Collagen
1	33	14	43	14.0	7.7
2	28	32	44	10.3	7.3
4	13	16	45	4.4	5.2
5	24	23.5	52	7.9	-
6	24	18	53	4.9	-
7	12	23	54	11.2	15.5
8	9.2	13.6	55	10.5	8.3
9	15	12	56	2.9	6.5
10	36	26	67	27.7	11.0
11	>30	22	68	13.6	7.5
12	5.6	4.7	75	3.8	5.4
15	21.5	16.6	76	14.3	10.5
16	12.5	4.1	77	4.3	2.9
17	7.7	5.0	78	6.2	8.3
18	6.6	3.2	79	4.3	5.1
21	30.9	-	80	7.4	10.9
22	41.3	-	81	5.5	7.0
24	6.4	-	85	17.7	14.4
25	11.1	6.6	86	6.2	5.3
26	16.5	9.5	91	9.7	6.7
29	9.0	8.1	92	7.3	6.5
32	3.5	3.8	93	18.3	8.7
33	11.9	12.5	94	8.0	6.9
34	8.2	6.6	95	15.4	2.5
37	21.2	17.8	96	3.9	3.7
38	9.0	4.6	97	16.0	3.2
39	>30	>30	98	11.2	8.8
40	11.3	13.2	103	18.5	6.7
41	4.2	5.1	papaverin	>100	>100

Experiment 2 [prolonging test of the bleeding time in mouse]

5 Six male ICR strain mice weighing 20 g for each group were administered orally with 300 mg/kg of the test drug (all the test drugs were used in the form of the suspension in 0.5% CMC). Two hours after administration, 5 mm of the tail from the top was cut under pentobarbital anesthesia, and the bleeding was observed by tapping at the cutting site with a filter paper every 15 seconds. The time when the bleeding was observed stopping for one minute is defined as the arrest point of bleeding, and the duration required from the time when the cutting was done to the arrest point of bleeding is defined as the bleeding time. The observation was carried out up to 1200 seconds. Ticlopidine was used as a positive control.

10 15 The results were shown in Table 2. The compound numbers in Table 2 correspond to those in the Examples described below.

Table 2

Compound No.	Bleeding time \pm standard error
53	270.0 \pm 54.08
56	277.5 \pm 36.90
ticlopidine	1127.5 \pm 72.50 (note)
the solvent	305.0 \pm 77.23

(Note) $P < 0.05$ by Mann and Whitney's U test.

30 The following Examples illustrate the method for preparing the compound of the present invention in more detail.

35 Example 1

Preparation of (E)-3-(2-oxopropylidene)-1,4-diphenyl-2-azetidinone (Compound 1)

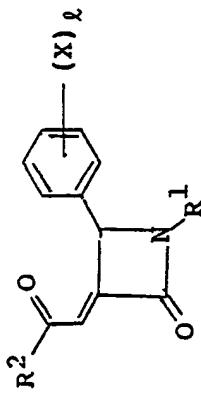
40 To a solution of 0.67 g of acetylmethylenetriphenylphosphorane in 70 ml of benzene was added at room temperature under a nitrogen atmosphere a solution of 0.50 g of 1,4-diphenyl-2,3-azetidinedione in 30 ml of benzene, and the mixture was stirred overnight. After completion of the reaction, the benzene was evaporated, and the residue was applied to silica gel column chromatography (eluent: methylene chloride). The desired fractions were combined, the solvent was evaporated, and the residue was recrystallized from ethanol to give the title compound as pale yellow needles. Yield 0.32 g, m.p. 157.5 - 158.5°C

45 Example 2

50 Following the similar procedure of that of Example 1, there were obtained the compounds 2 to 118, which were listed in Table 3 including the compound obtained in Example 1.

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Table 3



Compound No.	(X) ₂	R ¹	R ²	m.p. (°C)
1	H	phenyl	methy1	157.5-158.5
2	H	phenyl	ethyl	149-150.5
3	H	phenyl	ethoxy	130.5-132.5
4	H	phenyl	phenyl	226-227
5	H	phenyl	p-methylphenyl	174-177
6	H	phenyl	p-methoxyphenyl	227.5-228.5
7	H	phenyl	o,p-dimethoxy-phenyl	147.5-150
8	H	phenyl	p-fluorophenyl	222-223
9	H	phenyl	p-chlorophenyl	239.5-241
10	H	phenyl	p-bromophenyl	250.5-256

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Table 3 (Cont'd)

11	H	phenyl	250-250.5
12	H	p-nitrophenyl	235.5-236.5
13	H	amino	212-213
14	H	1-adamantyl	198.5-200
15	H	ethoxycarbonyl-methyl	154.5-159.5
16	H	p-methoxyphenyl	142-144
17	H	p-fluorophenyl	140.4-141.9
18	H	p-nitrophenyl	199.5-200.4
19	H	p-fluorophenyl	188-189.5
20	H	p-nitrophenyl	300 or above
21	H	p-methylphenyl	142-144
22	H	p-methoxyphenyl	147-148.5
23	H	p-fluorophenyl	172-174
24	H	p-nitrophenyl	195-196
25	H	2-methyl-5-chlorophenyl	149.5-151.5

- Cont'd -

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Table 3 (Cont'd)

26	H	2-methyl-5-chlorophenyl	phenyl	145-147
27	H	2-methyl-5-chlorophenyl	p-fluorophenyl	140-142
28	H	2-methyl-5-chlorophenyl	p-nitrophenyl	195.5-197
29	H	p-fluorophenyl	phenyl	206-208.5
30	H	p-fluorophenyl	p-fluorophenyl	211-213
31	H	p-fluorophenyl	p-chlorophenyl	221.5-224
32	H	p-fluorophenyl	p-nitrophenyl	204.5-207
33	H	o-fluorophenyl	p-fluorophenyl	180.5-183
34	H	o-fluorophenyl	p-nitrophenyl	219.7-221
35	H	o-chlorophenyl	p-fluorophenyl	146-147.5
36	H	o-chlorophenyl	p-nitrophenyl	189-191
37	H	3,5-dichlorophenyl	p-fluorophenyl	200.2-201.5
38	H	3,5-dichlorophenyl	p-nitrophenyl	206 (decomposition)
39	H	p-bromophenyl	p-methoxyphenyl	208-209
40	H	p-bromophenyl	p-fluorophenyl	211.5-213

- Cont'd -

55 45 46 48 50 55 35 38 25 20 10 5

Table 3 (Cont'd)

41	H	p-bromophenyl	222-224
42	H	o-methoxyphenyl	219-221.2
43	H	m-trifluoromethylphenyl	174-177
44	H	m-trifluoromethylphenyl	159.5-161
45	H	m-trifluoromethylphenyl	181.5-184
46	H	p-dimethylaminophenyl	168-170
47	H	p-carboxyphenyl	300 or above
48	H	p-dichloroacetylphenyl	180.5-183.5
49	H	p-dichloroacetylphenyl	190.5-192.5
50	H	benzyl	76.5-78.5
51	H	benzyl	111.5-113.5
52	H	benzyl	105-107.5
53	H	benzyl	122-126
54	H	o-chlorobenzyl	78-79
55	H	o-chlorobenzyl	74-76

- Cont'd -

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Table 3 (Cont'd)

56	H	o-chlorobenzyl	p-nitrophenyl	113-115
57	H	1(S)-phenethyl	p-nitrophenyl	127.5-130.5
58	H	1-carboxy-2-phenethyl	p-fluorophenyl	250-255
59	H	propyl	p-fluorophenyl	88.5-91
60	H	propyl	p-nitrophenyl	127.5-130.5
61	H	cyclohexyl	methyl	124-127
62	H	cyclohexyl	p-fluorophenyl	125-126.5
63	H	cyclohexyl	p-nitrophenyl	199-202.5
64	H	1,2-bis(methoxycarbonyl)- ethyl	p-fluorophenyl	126-128
65	p-methyl	phenyl	p-fluorophenyl	208.5-211
66	p-methyl	phenyl	p-nitrophenyl	240.5-242.5
67	p-ethyl	o-methylphenyl	p-fluorophenyl	143-144.2
68	p-ethyl	o-methylphenyl	p-nitrophenyl	157.2-158.6
69	o-methoxy	o-methylphenyl	p-fluorophenyl	133-135.5
70	o-methoxy	o-methylphenyl	p-nitrophenyl	178-180.5

	55	45	45	35	30	25	20	15	10	5
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Table 3 (Cont'd)

71	m-methoxy	phenyl	phenyl	p-fluorophenyl	173.5-176.2
72	m-methoxy	phenyl	phenyl	p-nitrophenyl	194.5-196.5
73	3,4-dimethoxy	phenyl	phenyl	p-fluorophenyl	164.5-169
74	3,4-dimethoxy	phenyl	phenyl	p-nitrophenyl	192-195
75	p-hydroxy	phenyl	phenyl	p-nitrophenyl	166.5-167.5
76	p-fluoro	phenyl	phenyl	p-fluorophenyl	209.5-211
77	p-fluoro	phenyl	phenyl	p-nitrophenyl	225-226
78	p-fluoro	o-methylphenyl	o-methylphenyl	p-fluorophenyl	157-159.5
79	p-fluoro	o-methylphenyl	o-methylphenyl	p-nitrophenyl	193-195.5
80	o-fluoro	phenyl	phenyl	p-fluorophenyl	191.3-192.2
81	o-fluoro	phenyl	phenyl	p-nitrophenyl	224.8-226.7
82	o-chloro	phenyl	phenyl	p-fluorophenyl	213.5-216
83	p-chloro	o-methylphenyl	o-methylphenyl	p-fluorophenyl	150-151.5
84	p-chloro	o-methylphenyl	o-methylphenyl	p-nitrophenyl	180-182
85	p-bromo	o-methylphenyl	o-methylphenyl	p-fluorophenyl	157.4-158.7

Table 3 (Cont'd)

			5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	
86	p-bromo	o-methylphenyl																					
87	o-bromo	phenyl																					
88	o-bromo	phenyl																					
89	p-cyano	o-methylphenyl																					
90	p-cyano	o-methylphenyl																					
91	H	p-methylbenzyl																					
92	H	p-methoxybenzyl																					
93	H	p-fluorobenzyl																					
94	H	o-methoxybenzyl																					
95	H	o-trifluoromethylbenzyl																					
96	H	o-fluorobenzyl																					
97	H	m-chlorobenzyl																					
98	H	p-chlorobenzyl																					
99	H	m-trifluoromethylbenzyl																					
100	H	p-trifluoromethylbenzyl																					

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Table 3 (Cont'd)

101	H	m-methoxybenzyl	p-nitrophenyl	124-126
102	H	3,4-methylenedioxybenzyl	p-nitrophenyl	148-151
103	H	2,4-dichlorobenzyl	p-nitrophenyl	96-98
104	H	3,4-dichlorobenzyl	p-nitrophenyl	145.5-148
105	H	1-naphthylmethyl	p-nitrophenyl	167.5-169
106	H	o-fluorobenzyl	p-fluorophenyl	96-97.5
107	H	m-methoxybenzyl	p-fluorophenyl	108-110.5
108	H	m-trifluoromethylbenzyl	p-fluorophenyl	100-102
109	H	p-trifluoromethylbenzyl	p-fluorophenyl	136-138
110	H	3,4-dichlorobenzyl	p-fluorophenyl	111-113
111	o-methyl	benzyl	p-nitrophenyl	111-114
112	p-methoxy	benzyl	p-nitrophenyl	127-128
113	p-fluoro	benzyl	p-nitrophenyl	118-120
114	m-chloro	benzyl	p-nitrophenyl	82-87
115	p-fluoro	o-chlorobenzyl	p-nitrophenyl	98.5-101.5

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Table 3 (Cont'd)

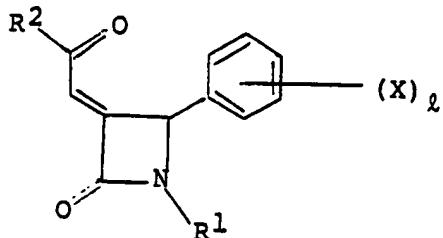
116	p-isopropyl	o-chlorobenzyl	p-nitrophenyl	155-156
117	o-fluoro	o-chlorobenzyl	p-nitrophenyl	153.5-157
118	p-trifluoro- methyl	o-chlorobenzyl	p-nitrophenyl	115.5-121.5

Claims

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1. 2-Azetidinone derivatives represented by the following formula

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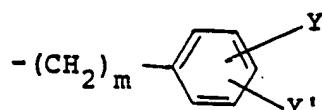


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wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, l is 1 or 2, R¹ is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula

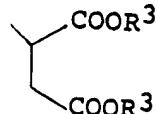
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(wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula

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(wherein R³ is a lower alkyl group), and R² is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxy carbonylmethyl group, or a group of the formula

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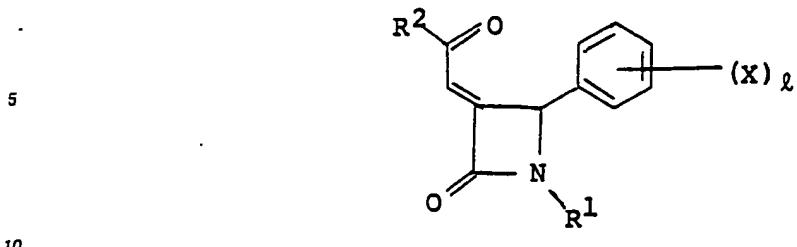


(wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

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2. Blood platelet aggregation inhibiting agents containing 2-azetidinone derivatives represented by the general formula

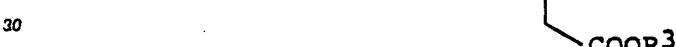
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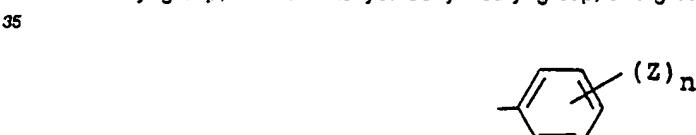
wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, l is 1 or 2, R1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula



25 (wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula



(wherein R3 is a lower alkyl group), and R2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxy carbonylmethyl group, or a group of the formula

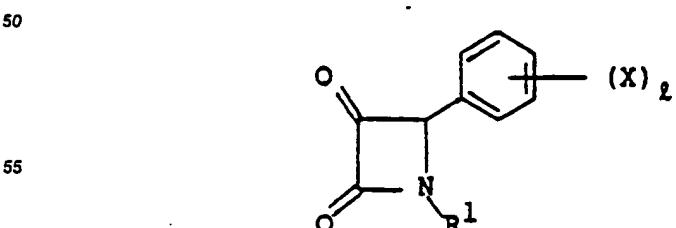


45 (wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

3. A 2-azetidinone derivative according to Claim 1, wherein the oxyalkylidene substituent has the E-configuration.

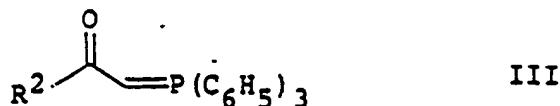
4. A 2-azetidinone derivative according to Claim 1 or Claim 3, wherein the configuration due to the asymmetric carbon atom at the 4-position is of the dl-form.

5. A process for producing a 2-azetidinone derivative of the formula given and defined in Claim 1, which comprises reacting a compound of the formula



II

wherein R¹, X and L are as defined in Claim 1, with a Wittig reagent of the formula



wherein R² is as defined in Claim 1.

10 6. A 2-azetidinone derivative of the formula given and defined in Claim 1 for use as a pharmaceutical.

7. A 2-azetidinone derivative of the formula given and defined in Claim 1 for use as a blood platelet aggregation inhibiting agent.

15 8. A pharmaceutical composition comprising a 2-azetidinone derivative of the formula given and defined in Claim 1 and a pharmaceutically acceptable diluent or carrier.

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DOCUMENTS CONSIDERED TO BE RELEVANT			EP 87308942.9
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	<p>TETRAHEDRON, vol. 41, no. 2, 1985</p> <p>MORI et al.: "New synthesis of β-lactames" pages 375-385</p> <p>* Pages 381, 385 (compounds 20a, 20b, 20c, 20c') *</p> <p>--</p>	1,3-5	C 07 D 205/08 A 61 K 31/395
A	<p>LIEBIGS ANNÄLEN DER CHEMIE, 1983, Heft 5</p> <p>H.-H. OTTO et al. "Darstellung und Stereochemie von 3-(α-Hydroxybenzyl)-1,4-diphenyl-2-azetidironen)" pages 1152-1168</p> <p>* Pages 1153, 1158 (compounds 3,5); pages 1165-1168 (compounds 4,4f,8) *</p> <p>--</p>	1,3-5	
A	<p>ARCHIV DER PHARMAZIE, vol. 319, no. 3, March 1986</p> <p>BERGMANN et al.: "Zur N- und C-Silylierung von β-Lactamen" pages 203-216</p> <p>* Pages 208, 214, 215 (compounds 14,15) *</p> <p>--</p>	1,3-5	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	<p>EP - A1 - 0 149 419 (NIPPON ZOKI PHARM.)</p> <p>* Page 1, last two lines; page 2; claims 15-19 *</p> <p>--</p>	2,6-8	C 07 D 205/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
VIENNA	07-01-1988	JANISCH	
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EUROPEAN SEARCH REPORT

Application number

EP 87308942.9

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages		
D,A	<p>TETRAHEDRON LETTERS, vol. 25, no. 42, 1984</p> <p>MANHAS et al.: "A convenient synthesis of azetidine-2,3-diones" pages 4733-6</p> <p>* Page 4735 *</p> <p>-----</p>	5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
	<p>The present search report has been drawn up for all claims</p>		
Place of search	Date of completion of the search	Examiner	
VIENNA	07-01-1988	JANISCH	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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